REMARKS

In the Specification

The specification is amended to explicitly recite that the application is a national stage application of PCT/EP99/07689, filed on October 13, 1999, which claims priority to U.S. provisional application 60/106,205, filed on October 30, 1998.

In the Abstract

An abstract on a separate page is attached.

Claim Objections and the Rejection Under 35 USC § 101

Claims 1-11 are amended. Amended claim 1, as with original claim 1, recites that components A, B and C are all present in the composition. The amendments to claim 1 do not narrow the scope of the claim. One of skill in the art reading the specification would have understood that all three active ingredients are comprised in the claimed composition. See, for example, page 6, lines 31-35, page 9, lines 1-3, page 11, lines 22-25, and Example 1. The remaining amendments to the claims are only cosmetic and do not change the scope of the claims. Claim 12 is cancelled without prejudice or disclaimer.

New Claim 13 is supported by, for example, Example 1. Dependent claims 14-28 are also added. Support, for example, for claim 14 can be found in original claim 1; for claim 15 on page 9, lines 10-12; for claim 16 on page 10, lines 26-27; for claim 17 on page 11, lines 4; for claim 18 on page 9, lines 1-3; for claim 19 in original claims 2, 3, and 5; for claim 20 in original claim 6; for claims 21-23 on page 7, lines 13-27; and for claims 24 to 28 in original claims 7-11. No new matter is added. Withdrawal of the claim objections and section 101 rejection is requested.

Rejections under 35 USC § 112, first paragraph

The Office Action alleges that while the specification is enabling with respect to the specifically named methylene and methyl donors recited in claim 2, and the specific methyl

transporters in claim 3, and the specific bioflavanoids of claim 6, it does not enable the terms methyl and methylene donors, methyl transporters and bioflavanoids in claim 1.

Nowhere does the law require an applicant to name all the species embraced by the scope of the claims. The specification in the instant case provides adequate guidance to one of skill in the art to determine the meaning and scope of the rejected terms. The specification provides an extensive list of exemplary methyl and methylene donors, methyl transporters and bioflavanoids in excess of what is claimed. See, for example page 4, lines 12-20; page 5, lines 6-7; page 6, lines 20-28; page 7, lines 1-3; page 7, lines 13-27; and page 8, lines 22-35.

The Office Action also alleges that applicants fail to set forth the criteria that define the characteristics of the terms. The specification clearly defines methyl donor, methylene donor, and methyl transporter by their function on page 6, lines 5-20. The term bioflavanoid is a term readily understood by those skilled in the art even without the numerous specific preferred biolfavanoids recited on page 8, lines 22-28.

The enablement rejection is thus unfounded. The specification provides ample teaching and guidance by both defining the rejected terms by function and by numerous specific examples to teach one of skill in the art to practice the claimed invention to its full scope.

The Office Action also alleges that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Based on this assertion, the Office Action concludes that undue experimentation is required to practice the claimed invention. Applicants' disagree.

A disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. See, e.g., *In re Brana*, 51 F.3d 1560 (Fed. Cir.1995). Applicants respectfully submit that it is the initial burden of the PTO to establish a reason to doubt the truth of the statements

presented in the specification concerning utility. See, e.g., *In re Marzocchi et al.,* 169 USPQ 367, 370 (CCPA 1971) ("...it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure....")

The Examiner has given no reason to doubt the objective truth of the statements of enablement in the application. The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of Section 112 requires nothing more than objective enablement, how such a teaching is set forth, either by use of the illustrative examples or by broad terminology, is of no importance. See, e.g., *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971).

The Office Action appears to suggest, through the citation of *Wands* and *Forman*, that undue experimentation is required to practice the invention. First, this analysis should not even be reached, in the absence of the "reasons or evidence" required under *Marzocchi.* Merely asserting that an art is unpredictable does not result in a conclusion of undue experimentation. See, e.g., *In re Angstadt*, 190 USPQ 214 (CCPA 1976). Second, as long as a skilled worker can make the compounds, he or she can routinely test them to determine their relative activity. Even if one of skill in the art needs to assess a specific composition, or a number of specific compositions, to practice the invention, that experimentation is not undue. Testing such specific compositions for their intended effect is routine. Even if considerable effort is required to assess a composition's activity, that is not undue experimentation because no inventive skill is required to routinely test said composition. This degree of effort is fully routine, being nothing more than that expended by skilled workers on a day-to-day basis in the field. It is by well settled law that the test for enablement is not whether any experimentation is needed but whether or not that experimentation is undue. See, e.g., *In re Angstadt*, at 219. Even a considerable amount of experimentation is permissible if it is routine. See, e.g., *Ex parte Jackson,* 217 USPQ 804, 807 (POBA 1982). Even if the experimentation needed is complex that does not necessarily make the experimentation undue under the enablement requirement. See also, for example, *In re Wands*, 8 USPQ 2nd 1400,

1404 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for routine experimentation."). Thus, undue experimentation is not present in the current situation, since one of ordinary skill in the art can easily, in view of what is already known in the art and in view of the guidance in the present specification, practice the invention using no more than routine experimentation. Accordingly, it can be seen that the full scope of the uses recited in the claims is enabled by the specification.

Furthermore, the Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 03/30/1995), held that

> "usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer."

Thus, Applicants are not required to not test each embodiment of the compositions for physiological activity to enable the claimed uses of the inventive composition. See also Angstadt.

Rejections under 35 USC § 112, second paragraph

Claims 7 and 12 were rejected for the recitation of the term "transmethylation disorders." Claim 12 is cancelled without prejudice or disclaimer.

The term "transmethylation disorders" is well defined in the specification and is also well recognized in the art. The specification teaches that a decrease of the pool of methyl donors and/or methyl transporters can lead to transmethylation disorders. See, e.g., page 4, lines line 7 to page 5, line 36. Applicants also provide a list below of citations related to transmethylation. Copies of each reference is not submitted because the title of the cited

references themselves are adequate to demonstrate that the term is well known by those skilled in the art. Claim 7 is thus not indefinite. The citations follow:

- R. Vetter et al., Interactions between cyclic AMP-dependent protein phosphorylation and lipid transmethylation reactions in isolated porcine cardiac sarcolemna, Mol. Cell. Biochem., 1989 Nov 23, 91(1-2), 51-61.
- T. Bottiglieri et al., Transmethylation in depression, Ala. J. Med. Sci., 1988 Jul, 25(3), 296-301.
- C. Prasad et al., Biocemical transmethylation of lipids and neuropeptidergic stimulation of pituitary hormone secretion, Brain Res., 1985 May 13, 334(1), 41-6.
- V.M. Andreoli et al., Transmethylations and the central nervous system: introduction, Monogr.Gesamtgeb. Psychiatr. Psychiatry Ser., 1978, 18, 1-3.
- J.D. Smith, Regulation of transmethylation by an S-adenosylmethionine binding protein, Biochem. Biophys. Res. Commun., 1976 Nov 8, 73(1), 7-12.
- J.K. Coward, A mechanistic study of biological transmethylation, Psychopharmacol. Bull., 1975 Apr, 11(2), 41.
- A. Rigoli, Biological transmethylations, Farmaco [Prat], 1973 Aug, 28(8), 658-74.
- Transmethylation (1979), E. Udsin, R.T. Borchardt, C.R. Creveling (Eds.), Developments in neuroscience, vol. 5, New York, Amsterdam, Oxford, Elsevier.
- Transmethylations and the central nervous system (1978), Psychiatry series, V.M. Andreoli, A. Agnoli, C. Fazio (Eds.), Berlin, Springer-Verlag.
- Transmethylation and methionine biosynthesis (1965), S.K. Shapiro, F. Schlenk (Eds.), Chicago, London, University of Chicago Press.
- R.M. Hoffmann, Methioninase: a therapeutic for diseases related to altered methionine metabolism and transmethylation: cancer, heart disease, obesity, aging, and Parkinson's disease, Hum. Cell. 1997 Mar, 10(1), 69-80.
- J.M. Scott et al., Effects of the disruption of transmethylation in the central nervous system: an animal model, Acta Neurol. Scand. Suppl. 1994, 154, 27-31.
- R.M. Hoffmann, Unbalanced transmethylation and the perturbation of the differentiated state leading to cancer, Bioassays, 1990 Apr, 12(4), 163-6.
- P.S. Prytz et al., Differential cell cycle perturbation by transmethylation inhibitors, Biochem. Pharmacol., 1990 Jan 1, 39(1), 203-6.

Rejections under 35 USC § 102

Claims 1-2 and 5-12 were rejected as allegedly anticipated by Strydon and claims 1, 3-4 and 7-11 were rejected as allegedly anticipated by La Greca.

None of these references teach all three components of the claimed composition. Thus, there is no anticipation.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To Show Changes Made**".

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Version With Markings To Show Changes Made

In the Abstract

The existing Abstract has been replaced with the attached Abstract of the Disclosure, therefore no marked up version is necessary.

In the Claims

The claims have been amended as follows:

1. (Amended) ~~Composition~~ A composition comprising ~~one or more active ingredients and, optionally, one or more nutritional substances, solid, liquid and/or semiliquid excipients or auxiliaries, characterized in that the active ingredients consist of~~

~~a)~~ a component A ~~consisting of~~ comprising one or more compounds ~~selected from~~ that are methyl ~~and~~ or methylene donors,

~~b)~~ a component B ~~consisting of~~ comprising one or more methyl transporters, and

~~c)~~ a component C ~~consisting of~~ comprising one or more bioflavonoids.

2. (Amended) ~~Composition~~ A composition according to claim 1, ~~characterized in that~~ wherein component A ~~consists of~~ comprises one or more compounds selected from the group consisting of betaine, dimethylglycine, sarcosine and serine, ~~or~~ and their physiologically acceptable salts.

3. (Twice Amended) ~~Composition~~ A composition according to claim 1, ~~characterized in that~~ wherein component B ~~consists of~~ comprises one or more compounds selected from the group consisting of dihydrofolic acid, tetrahydrofolic acid, 5-methyltetrahydrofolic acid, 5-formyltetrahydrofolic acid, 10-formyltetrahydrofolic acid, 5,10-methylenetetrahydrofolic acid, and 5,10-methenyltetrahydrofolic acid, ~~or~~ and their physiologically acceptable salts.

4. (Amended) ~~Composition~~ A composition according to claim 3, ~~characterized in that~~ wherein component B ~~consists of~~ comprises L-5-methyltetrahydrofolic acid or a physiologically acceptable salt thereof.

5. (Twice Amended) ~~Composition~~ A composition according to claim 1, ~~characterized in that~~ wherein component C ~~consists of~~ comprises one or more compounds selected from the group consisting of mono-, di- ~~or~~ and triglycoside bioflavonoids ~~containing the~~ that contain an aglycone quercetin.

6. (Amended) ~~Composition~~ A composition according to claim 5, ~~characterized in that~~ wherein component C ~~consists of~~ comprises one or more compounds selected from the group consisting of isoquercetin, quercetin, isoquercitrin, quercimeritrin, spiraeosid, rutin, and hyperin.

7. (Twice Amended) ~~Composition according to claim 1 for the treatment and prevention of~~ A method of treating or preventing a transmethylation disorders comprising administering to a patient in need thereof an effective amount of a composition according to claim 1.

8. (Twice Amended) ~~Composition according to claim 1 for the treatment and prevention of~~ A method of treating or preventing a cardiovascular diseases comprising administering to a patient in need thereof an effective amount of a composition according to claim 1.

9. (Twice Amended) ~~Composition according to claim 1 for the treatment and prevention of~~ A method of treating or preventing an atherogenic and/or thrombogenic

diseases comprising administering to a patient in need thereof an effective amount of a composition according to claim 1.

10. (Twice Amended) ~~Composition according to claim 1 for the treatment and prevention of~~ A method of treating or preventing a diseases associated with hyperhomocysteinemia comprising administering to a patient in need thereof an effective amount of a composition according to claim 1.

11. (Twice Amended) ~~Composition according to claim 1 for the treatment and prevention of~~ A method of treating or preventing premature occlusive arterial disease, severe vascular disease in infancy and childhood, progressive arterial stenosis, intermittent claudication, renovascular hypertension, ischemic cerebrovascular disease, premature retinal artery and retinal vein occlusion, cerebral occlusive arterial disease, occlusive peripheral arterial disease, premature death due to thromboembolic disease and/or ischemic heart disease, comprising administering to a patient in need thereof an effective amount of a composition according to claim 1.

Claim 12 has been cancelled without prejudice or disclaimer.

Claims 13-28 have been newly added.